Office Action Summary	Application No.	Applicant(s)	
	10/531,966	WITTWER ET AL.	
	Examiner	Art Unit	
	Suryaprabha Chunduru	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-20,23-30,33-35,37,39,40,43,45-51,53,55-58,61,65,66 and 83-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *49-51,53,55-58 and 61* is/are allowed.

6)☒ Claim(s) *18-20,23-30,33-35,39,40,45-48,83 and 86* is/are rejected.

7)☒ Claim(s) *26,28,84 and 85* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *12/18/08* .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The response to the office action filed on December 19, 2008 has been considered and acknowledged.

Status of the Application

2. Currently claims 18-20, 23-30, 33-35, 37, 39-40, 43, 45-51, 53, 55-58, 61, 65-66, 83-86 are under examination. New claims 83-86 are added. Claims 1-17, 21-22, 31-32, 36, 38, 41-42, 44, 52, 54, 59-60, 62-64, 67-82 were cancelled. Claims 24, 26, 28, 29-30, 45, 49 are amended. All arguments and amendment have been fully considered and thoroughly reviewed and deemed persuasive in-part in view of the amendment. The action is made FINAL necessitated by the amendment.

New Grounds of rejections necessitated by Amendment

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 30 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The instant claim recites DNA dye having at least 50% saturation (BO-PRO-1). The independent claim 24, upon which the instant claim depends requires DNA dye having at least 90% saturation. Thus the meets and bounds of the claim are unclear and indefinite because it is not clear whether the claim requires dyes that possess 90% saturation or not, as amended in claim 24.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claim 86 is rejected under 35 U.S.C. 102(a) as being anticipated by Elenitoba-Johnson (US 6,346,386).

Elenitoba-Johnson teaches a method of claim 86, of PCR analysis comprising providing a mixture of a target nucleic acid, PCR reagents, oligonucleotide primers configured for amplifying the target nucleic acid and a dsDNA binding dye, amplifying nucleic acid in the presence of the dye and monitoring the amplified nucleic acid by generating the melting curves from the amplified target nucleic acid using fluorimeter, normalizing the melting curve, repeating the providing amplifying normalizing and generating steps with at least one additional target nucleic acid and comparing the normalized melting curves and plotting the fluorescence difference between the normalized curves superimposing a portion of the curve and plotting the fluorescence difference between the curves (see col. 3, line 6-67, col. 4, line 1-67, col. 5, line 1-5, col. 6, line 35-54). Accordingly claim 86 is anticipated.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

A. Claims 18-19, 20, 23-25, 27, 29-30, 33-35, 37, 39-40, 43, 45-48, 83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elenitoba-Johnson (US 6,346,386) in view of Erikson et al (US 6,927,027).

Elenitoba-Johnson teaches a method of claim 18-19, 24-25, 45-46, of PCR analysis comprising providing a mixture of a target nucleic acid, PCR reagents, oligonucleotide primers configured for amplifying the target nucleic acid and a dsDNA binding dye having percent saturation of at least 90%, amplifying nucleic acid in the presence of the dye and monitoring the amplified nucleic acid by generating the melting curves from the amplified target nucleic acid using fluorimeter, normalizing the melting curve, repeating the providing amplifying normalizing and generating steps with at least one additional target nucleic acid and comparing the normalized melting curves and plotting the fluorescence difference between the normalized curves superimposing a portion of the curve and plotting the fluorescence difference between the

curves (see col. 3, line 6-67, col. 4, line 1-67, col. 5, line 1-5, col. 6, line 35-54).

With regard to claim 20, 23, Elenitoba-Johnson teaches that the target nucleic acid comprises single nucleotide polymorphism and the method comprises mutational scanning and identifies resultant hetero and homoduplexes (see col. 3, line 6-67, col. 4, line 1-67, col. 5, line 1-5, col. 6, line 35-54).

With regard to claim 26-28, 47-48, Elenitoba-Johnson teaches that the method comprises the step of plotting the fluorescence difference between normalized curves, and plotting temperature shifted curves (see col. 3, line 41-50, col. 4, line 57-67, col. 5, line 1-5, col. 7, line 18-30).

With regard to claims 37, 39-40, 43, Elenitoba-Johnson teaches that the target nucleic acid comprises two melting domains and the method comprises repeating mixing, amplifying and melting steps with one additional target nucleic acid, comparing the melting curve for the target nucleic acid with the melting curve for the additional target nucleic acid (see col. 3, line 6-50, line 62-67, col. 4, line 1-44).

However Elenitoba-Johnson specifically did not teach saturating dyes as claimed in claims 29-30, excitation and emission maximum in a range of 410-465nm and 450-500 nm.

Erikson et al. teach a method for nucleic acid multiplex formation wherein the method comprises the use of DNA binding intercalator dyes as accelerator agents, that are selected from the group consisting of PO-PRO-1, JO-PRO-1, SYTOX, SYTO dyes, YOYO-3, TOTO-3 (see col. 7, line 14-30). Erikson et al. also teach use of a probe in said method (see col. 3, line 46-61, col. 11, line 41-48) and the excitation and emission wavelength of the dyes ranging from 200 to 1000nm and excitation maximum and measuring the magnitude difference using argon ion laser

based fluorimeter (see col. 11, line 49-51, col. 24, line 57-65, col. 16, line 38-46, col. 23, line 52-65).

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of monitoring amplification of a target nucleic acid during PCR in the presence of a dsDNA binding dye as taught by Elenitoba-Johnson with a step of including accelerator agents that enhance the specificity of the signal detection as taught by Erikson et al. for the purpose of developing an improved real-time amplification method. One skilled in the art would be motivated to combine the references because an ordinary artisan skilled in the art would have a reasonable expectation of success that the method would result in enhancing the specificity because Erikson et al. explicitly taught the use of the intercalating agents as accelerators that enhance the specificity of probe-target binding and the signal generated by the intercalating agents is directly correlated to the probe-target binding thereby increasing the extent of matching between probe and the target (see col. 16, line 47-63) and such modification of the method would be obvious over the cited prior art.

B. Claims 65-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elenitoba-Johnson (US 6,346,386) in view of Erikson et al (US 6,927,027) further in view of Nurmi et al (Anal. Biochem., Vol. 299, pp. 211-217, December, 2001).

Elenitoba-Johnson in view of Erikson et al. teach a method of PCR analysis as discussed above in section 5A.

However neither Elenitoba-Johnson nor Erikson et al. specifically teach target nucleic acid comprising a locus of HLA gene.

Nurmi et al. reach a PCR analysis in the presence of a ds binding dye and a probe wherein the method comprises a target nucleic acid comprising HLA gene (see page 213, col. 1, paragraph 1 under all-in-one dry reagent concept, page 215, col. 1, line 2-27, col. 2, paragraph 2).

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of monitoring amplification of a target nucleic acid during PCR in the presence of a dsDNA binding dye as taught by Elenitoba-Johnson in view of Erikson et al. with a step of including a highly polymorphic HLA gene as a target nucleic acid as taught by Nurmi et al. for the purpose of detecting single nucleotide polymorphisms. One skilled in the art would be motivated to combine the method as disclosed by Elenitoba-Johnson in view of Erikson et al. with target HLA gene as taught by Nurmi et al. because Nurmi et al. explicitly taught the real-time monitoring of HLA gene target in the presence of a dsDNA binding dye would eliminate false positives and since detection of SNPs is very useful in linkage and disease marker association studies, the method provides highthrouput analysis of SNPs (see page 215, col. 1, line 2-27, col. 2, paragraph 2). The ordinary artisan would have had a reasonable expectation of success that inclusion of inclusion of said target would result in a high throughput analysis of highly polymorphic loci such as HLA gene as suggested by Nurmi et al. and such modification of the method would be obvious over the cited prior art.

Response to arguments:

6. With regard to the rejection of claims 2, 20, 23-28, 37, 39-40, 43, 45-48 under 35 USC 102(a) as being anticipated by Elenitoba-Johnson, Applicants' arguments and the amendment were fully considered and found persuasive in view of the amendment and the rejection is withdrawn.

7. With regard to the rejection of claims 3, 18-19, 29-30, 33-35 under 35 USC 103(a) as being unpatentable over Elenitoba-Johnson in view of Erikson et al., Applicants' arguments were fully considered and found unpersuasive. Applicants argue that Erikson et al. does not teach Fluorimeter and a dye having excitation and emission maxima in a different set of defined ranges and the combination of Elenitoba-Johson and Erikson et al. does not teach or suggest the instant claims 18-19. Applicants further argue that claim 24 is amended to recite saturation dye having at least 90% and the combination does not teach said limitation. Further Applicants assert that Erikson et al. uses a single probe and two melting domains as opposed to the instant claims that require single melting domain. Applicants' arguments were found unpersuasive. First, Elenitoba-Johnson teach use of fluorimeter analysis using DNA binding dyes. Erikson et al. also taught argon ion based laser fluorimeter to measure the fluorescence of saturation dyes. Erikson et al. also taught DNA dyes having 90% or higher saturation and measuring the excitation and emission maximum (see at least col. 24, line 57-65, which clearly teach the claimed wavelength ranges of excitation range as claimed). Further, the amendment of claims 29-30 does not over come the rejection, since Erikson et al. does teach DNA binding dyes having at least about 90% saturation as required by the instant amended claims. With regard to the melting domain, Examiner notes that the instant claims are in open 'comprising' format and as noted in MPEP 2111.03, any unrecited elements are steps are within the scope of the claims, thus the claims do not exclude having two melting domains as recited in Erikson et al. Accordingly the rejection is maintained and re-written to address the amended claims.

8. With regard to the rejection of claims 65-66 under 35 USC 103(a) as being unpatentable over Elenitoba-Johnson in view of Nurmi, Applicants arguments and the amendment were fully considered and found persuasive in view of the amendment and the rejection is withdrawn.

9. With regard to the rejection of claims 24, 49-50, 53, 55-58, 61 under double-patenting over patent 7, 387, 887, Applicants arguments and the amendment were fully considered and found persuasive and the rejection is withdrawn in view of the amendment and arguments.

Allowable Subject Matter

10. Claims 26, 28, and 84-85 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

***Conclusi*on**

Claims 49-51, 53, 55-58, 61 are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 571-272-0783. The examiner can normally be reached on 8.30A.M. - 4.30P.M, Mon - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Suryaprabha Chunduru/

Primary Examiner, Art Unit 1637